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EXAMINER	
KIM, YOUNG J	
ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/662,003	LEE ET AL.	
	Examiner	Art Unit	
	Young J. Kim	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-65* is/are pending in the application.

4a) Of the above claim(s) *51,52 and 57-65* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-50 and 53-56* is/are rejected.

7)☒ Claim(s) *25,34,35,43 and 44* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/11/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I, claims 25-50 and 53-65, the species A(iv) and A(ii), and SEQ ID Numbers 3, 4, and 12 in the reply filed on November 3, 2005 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 51 and 52 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention (i.e., Group), there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on November 3, 2005.

Newly submitted claims 57-65 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the elected invention for prosecution is drawn to a method for detecting the presence of a myostatin variant nucleic acid in a subject, wherein the detection of the myostatin variant in a subject is correlated with increased muscle mass or its predisposition. This invention requires that the variant nucleic acid sequence responsible for increasing muscle mass is already known, and hence, its detection leads to the correlation. The invention defined by claims 57-65, however, are different in that the method identifies a mutation in a gene encoding myostatin protein, but the detection does not result in any correlation. Hence, the method is reasonably drawn to a screening method which screens for mutation which are responsible for increased muscle mass.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 57-65 withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Reconsideration and rejoinder

With regard to claims 29, 30, 38-40 (drawn to non-elected species), said claims are rejoined as the present office action necessitates the consideration of the withdrawn species.

With regard to the SEQ ID Number restriction requirement, it is acknowledged that Applicants have elected SEQ ID Numbers 3, 4, and 12.

Upon careful review of the application, it appears that the search of SEQ ID Number 1, 2, and 8 would not result in an undue burden since SEQ ID Numbers 1 and 2 are complementary sequence of the elected SEQ ID Number 3, and 4; and SEQ ID Number 8 is the complementary sequence of the elected SEQ ID Number 12.

SEQ ID Numbers 6 and 10 are also rejoined as being drawn to the myostatin sequence of Belgian Blue bovine species.

To reiterate, the restriction requirement drawn to SEQ ID Numbers 1, 2, 6, 8, and 10 are hereby withdrawn and will be examined together.

However, SEQ ID Numbers 5, 7, 9, and 11 remain withdrawn from further consideration as being drawn to non-elected invention (i.e., SEQ ID Number).

Priority

The effective filing date of the instant application is determined to be November 10, 1997 (of the parent application serial no. 08/967,089).

While the parent applications disclose the polynucleotide, GSF8 (growth and differentiation factor, now known as myostatin), do not disclose any variants (mutants) which are responsible for increased muscle mass in non-human subjects. Applicants are invited to point to a specific page and

line number of the specification of the parent applications where such support would be found so as to be entitled priority.

Drawings

The drawings received on September 11, 2003 are acceptable.

Information Disclosure Statement

The IDS received on September 11, 2003 is acknowledged.

A signed copy of the PTO-1449 and forms listing the art of record are enclosed herewith.

Claim Objections

Claims 34, 35, 43, and 44 are objected to for reciting non-elected inventions (SEQ ID Numbers.

Claim 25 contains a typographical error in the phrase, "indicative of a increased muscle mass." The phrase should read, "indicative of an increased muscle mass."

Appropriate correction is required.

Specification

The specification fails to comply with the Sequence Requirement as set forth in 37 CFR 1.821-1.825. Specifically, Figure 1C discloses nucleotide sequences which comprise more than 10 consecutive nucleotides without their SEQ ID Identifier.

Sine the present application has a sequence listing of record, Applicants are requested to amend the specification to properly identify the nucleotide sequences in Figure 1C.

If the sequence listing as filed does not have the disclosed sequences, then Applicants must file: a) a new paper copy of Sequence Listing; b) a new CRF; and c) a statement according to 37 CFR 1.821(e).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 25-28, 31-37, 41, 42, and 54-56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 25 is indefinite for reciting the phrase, "a non-human subject having increased muscle mass or having a predisposition for increased muscle mass as compared to a subject having a wild-type nucleic acid sequence..." because it is unclear whether "a" subject (underlined) is also limited to a non-human subject or embraces a human subject. For the purpose of prosecution, the former interpretation is assumed.

Claim 26 recites the phrase, "further comprises amplifying the nucleic acid." The parent claim 25 recites two different types of nucleic acids – myostatin variant nucleic acid sequence and wild-type nucleic acid sequence. It is unclear to which nucleic acid the recited phrase finds antecedent basis. For the purpose of prosecution, the nucleic acid sequence is assumed to be myostatin variant nucleic acid sequence.

Claims 26-28, 31-37, 41, 42, and 54-56 are indefinite by way of their dependency on claim 25.

Claim 28 is rejected as being indefinite for reciting a sequence by its GenBank Accession Number AFO19620. Initially, the accession number is AF019620. Additionally, referring to a nucleotide sequence only by its accession number becomes indefinite because the nucleotide sequences found in GenBank constantly goes through sequence revisions.

For example, GenBank accession no. GI50593115 shows over twenty revisions, some of which include addition of sequences.

Applicants are invited to submit the actual sequence employed in their invention as well as a declaration stating that the submitted sequence is the same sequence employed at the time the application was filed, also complying the sequence rules as set forth in 37 CFR 1.821-1.825.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 25-42 and 54-56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for detecting the presence of a target myostatin variant nucleic acid sequence in a nucleic acid-containing specimen, wherein the specimen is bovine, said bovine being Belgian Blue or Piedmontese, said specimen having increased muscle mass or having a predisposition for increased muscle mass as compared to said specimen having a wild-type myostatin nucleic acid sequence, said method comprising detecting the presence of the target myostatin variant nucleotide sequence, wherein the target myostatin variant nucleotide sequence is a deletion of nucleotides 937-947 in myostatin gene of Belgian Blue; or wherein the target myostatin variant nucleotide sequence is a G to A substitution at nucleotide position 1056 in myostatin gene of Piedmontese, wherein said variant nucleotide sequence is found in both alleles (homozygous), does

not reasonably provide enablement for a method for detecting the presence of a target myostatin variant nucleic acid sequence in a nucleic acid specimen, wherein the specimen is avian, ovine, piscine, baboon, murine, or porcine, wherein the target myostatin variant nucleotide is any variant myostatin sequence, and wherein the variant sequence is found in only one allele (heterozygous). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation are summarized in In Re Wands (858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)). They include (A) the quantity of experimentation necessary, (B) the amount of direction or guidance presented, (C) the presence or absence of working examples, (D) the nature of the invention, (E) the state of the prior art, (F) the relative skill of those in the art, (G) the predictability or unpredictability of the art, and (H) the breadth of the claims.

Breadth of the Claims:

The breadth of the claims embrace a method of detecting the presence of any variant nucleic acid sequence (homozygous/heterozygous, insertion, deletion, polymorphism, substitution) in a myostatin gene of any non-human subject, wherein the presence of the detection correlates with an increased muscle mass or predisposition for increased muscle mass in said subject.

Whether the application as filed entitles the Applicants for the breadth of the claims covering the above, without requiring of a skilled artisan undue experimentation, is the subject of the present rejection.

Nature of the Invention:

The nature of the invention relates to a method of detecting/diagnosing for a particular mutation (or sequence variance) in a subject, which is correlated with a particular phenotype, in the present case, an increased muscle mass in said subject. As it is well known and established in the art, a particular mutation found in a specific species producing a particular phenotype, cannot, without exception, be assumed to be the same in other species.

Amount of direction/guidance & presence of working examples:

The instant specification discusses the implication of myostatin in muscle development (page 4, lines 23-25). The specification discloses that the individual muscles in myostatin null mice weighs 2 to 3 fold more than its wild-type (page 2, lines 17-19).

The specification, in describing their invention, discloses that the deletion of nucleotides 937-947 in the third exon of the myostatin gene, is found in nucleic acid isolated from Belgian Blue cattle (page 5, lines 3-4), wherein the deletion is responsible for producing a frame-shift that results in a truncated protein (page 5, lines 5-6).

The specification also discloses that the substitution of the nucleotide G to the nucleotide A in exon 3 (page 2, lines 10-11), more particularly, at nucleotide position 1056 (Figure 1C and page 31, lines 10-11) in Piedmontese.

The specification discloses that the above two mutations are found in subjects (Belgian Blue and Peidmontese) which exhibit increased muscle mass while not present in subjects which exhibit non-doubled muscle mass (page 33, line 25-28 and page 34, lines 6-10).

The specification also discloses that the two mutations were homozygous mutations (i.e., present in both alleles; see page 34, lines 4-5 and lines 13-15).

While the specification contemplates that there is a high degree of sequence conservation of myostatin across species (page 33, lines 1-2), the instant specification only shows working examples

drawn to the above mutations for specific species of genus, bovine. No other myostatin variance sequences from other species which are correlated with increased muscle mass are disclosed.

The State of prior art & Unpredictability:

McPherron et al. (PNAS, November 1997, vol. 94, pages 12457-12461) evidences that a mutation present in one species responsible for a particular phenotype is not necessarily found in other species of the same genus. McPherron et al. demonstrates that a mutation found in a bovine species, Belgian Blue exhibiting increased muscle mass phenotype is not found in the bovine species, Piedmontese exhibiting the same phenotype. Similarly, the mutation responsible for increased muscle mass phenotype in Piedmontese is not present in Belgian Blue.

Hence, it is clear that correlation of a genotype to a particular phenotype is highly unpredictable and requires empirical determination for each of the species. While a region of myostatin gene might be highly conserved across species, not all mutations are conserved across species. McPherron et al. clearly evidences this fact in that two species of the same genus (bovine) exhibiting a same phenotype (increased muscle mass) comprises mutually exclusive mutation in myostatin gene.

Skill Level:

The skill level of the artisan is deemed high.

Amount of Experimentation:

One of skilled in the art, in order to practice the full scope of the invention would need to first identify mutations which are present in all non-human species, and particularly for avian, ovine, piscine, baboon, murine, porcine, and turkey, the mutations of which are responsible for producing increased muscle mass in each of the species. As the instant specification does not give any guidance to species other than that of the bovine, one of skill in the art must conduct empirical

experimentation of each of the species, the experimentation of which must consider a reasonable number of samples so as to produce a statistically significant result, the experimentation of which considers both homozygous and heterozygous mutations, amounting to an undue amount of experimentation to practice the invention commensurate in scope of the claims.

Claims 25-42 and 54-56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claims embrace a method of detecting the presence of target myostatin variant nucleic acid sequence in non-human specimen, as well as specimen being ovine, avian (turkey), any food products, said subject having an increased muscle mass or having predisposition for increased muscle mass as compared to a subject having a wild-type nucleic acid sequence wherein the presence of the variant nucleic acid sequence is indicative of the increased muscle mass (or its predisposition).

The instant specification only discloses two mutations, one (11 bp deletion) of which is drawn to Belgian Blue (bovine) and the other (G1056A substitution) drawn to Piedmontese (bovine), the mutations of which are indicative of increased muscle mass experienced by the two species of bovine.

The specification absolutely lacks examples drawn to mutations responsible for increased mutation experienced by the large genus embraced by, "non-human" subjects, including avian, ovine, and food products.

While the specification discloses that the nucleic acid encoding GDF8 (growth and differentiation factor 8), also known as myostatin is conserved among many organisms, it is clear from the examples of the instant specification that the mutations responsible for producing a phenotype are not conserved. For example, Piedmontese cattle and Belgian Blue both exhibit a same phenotype, that is, increased muscle mass. However, the mutations found on these two bovine species responsible for the phenotype are mutually exclusive. It is clear that even within the same bovine species, mutations producing a particular phenotype is not conserved. Hence, is reasonable to expect that the mutations causing increased muscle mass in species other than bovine, broadly embraced by the term, "non-human" which includes avian, ovine, food products, would also not be conserved and possibly mutually exclusive of each other. Since the method requires that the nucleic acid variant (mutant sequence) responsible for producing increased muscle mass be known, and since the specification absolutely lacks description of such sequences in species other than Belgian Blue and Piedmontese, claims lack written description of the genus, for lacking: a representative number of species embraced by the claims, and thus one of skill in the art would not readily recognize that artisans were in possession of the claimed invention at the time the application was filed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international

> application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 25-30, 33, 36, 37, 40, 42, and 54-56 are rejected under 35 U.S.C. 102(a) as being anticipated by Kambadur et al. (Genome Research September 1997, vol. 7, no. 9, pages 910-916).

Kambadur et al. disclose a method of detecting the presence of a target myostatin variant nucleic acid sequence from a bovine sample (Belgian Blue and Piedmontese; page 915, 1st column, bottom paragraph; and page 915, 2nd column 1st paragraph), wherein the artisans identify 11 base pair deletion in Belgian Blue myostatin gene and G to A substitution in exon 3 of Piedmontese myostatin gene (Abstract; page 914, 1st column), mutations which are homozygous and responsible for increased muscle mass (page 914, 1st column).

The detection is achieved by amplifying a segment containing the mutation from a myostatin gene via use of primers flanking the mutation (page 915, 2nd column 3rd paragraph) and sequencing the amplified product (page 915, 2nd column, 4th paragraph), thereby clearly anticipating claims 25-28 and 42.

With regard to claim 29, the artisans explicitly state that the 11-bp deletion would result in a truncated encoded protein (page 914, 1st column; also see Figure 1C; and page 913 for its description).

With regard to claim 30, while the artisans state that G to A substitution occurs at position 941 of the coding region, it appears that the mutation is the same mutation.

With regard to claim 33, northern analysis is performed with labeled byostatin cDNA probe (page 915, 2nd column, 5th paragraph).

With regard to claims 36, 37, 40, and 54, Belgian Blue and Piedmontese are of the bovine species.

With regard to claims 55 and 56, the samples employed by the artisans is biceps femoris muscle which inherently comprises skeletal muscles (page 915, 1st column, bottom paragraph).

Therefore, the invention as claimed is clearly anticipated by Kambadur et al.

Claims 25-29, 33, 36, 37, 40, 42, and 54-56 are rejected under 35 U.S.C. 102(e) as being anticipated by Grobet et al. (U.S. Patent No. 6,103,466, issued August 15, 2000, filed July 14, 1997).

Grobet et al. disclose a method of detecting the presence of mutation in myostatin gene, from a subject wherein the presence of said mutation is correlated with the subject having an increased muscle mass (column 2, lines 63-65; column 2 line 66 to column 3, line 11), wherein the method comprises the steps of detecting the presence of a mutation in myostatin gene (column 3, lines 13-22).

With regard to claim 26, the method comprises the step of amplifying the nucleic acid harboring the mutation (column 3, line 18-20; column 10, lines 66-67).

With regard to claim 27, the artisans explicitly state that, "primer pairs flanking the deletion [mutation] ...were prepared." (column 10, lines 66-67).

With regard to claim 28, the mutation is an 11-base pair nucleotide deletion (see Figure 2A; column 2, line 61; and column 11, lines 8-9).

With regard to claim 29, the deletion of the 11-base pair is disclosed as producing a truncated protein (column 10, lines 56-60), wherein the deletion causes a frame-shift resulting in a premature stop-codon after 13 encoded amino acids.

With regard to claim 33, the artisans also disclose that a probe is hybridized to the site of the mutation for detection (column 14, lines 37-38).

With regard to claims 36, 37, 40, and 54, the subject is Belgian Blue, a species of bovine (column 4, line 58; column 11, lines 8-9; column 14, line 42).

With regard to claim 42, the 11-base pair is disclosed being homozygous (column 11, lines 9-10).

With regard to claims 55 and 56, the specimen is a skeletal muscle tissue (claims 10 and 11 on column 59).

Therefore, the invention as claimed is clearly anticipated by Grobet et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 34, 35, and 43-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grobet et al. (U.S. Patent No. 6,103,466, issued August 15, 2000, filed July 14, 1997).

Grobet et al. disclose a method of detecting the presence of mutation in myostatin gene, from a subject wherein the presence of said mutation is correlated with the subject having an increased muscle mass (column 2, lines 63-65; column 2 line 66 to column 3, line 11), wherein the method comprises the steps of detecting the presence of a mutation in myostatin gene (column 3, lines 13-22).

The method comprises the step of amplifying the nucleic acid harboring the mutation (column 3, line 18-20; column 10, lines 66-67).

The artisans explicitly state that, "primer pairs flanking the deletion [mutation] ...were prepared." (column 10, lines 66-67).

The mutation is an 11-base pair nucleotide deletion (see Figure 2A; column 2, line 61; and column 11, lines 8-9).

The deletion of the 11-base pair is disclosed as producing a truncated protein (column 10, lines 56-60), wherein the deletion causes a frame-shift resulting in a premature stop-codon after 13 encoded amino acids (see Figure 1C; and page 913 for its description).

The artisans also disclose that a probe hybridization to a site of the mutation is also employed for detection (column 14, lines 37-38).

The subject is Belgian Blue, a species of bovine (column 4, line 58; column 11, lines 8-9; column 14, line 42).

The 11-base pair is disclosed being homozygous (column 11, lines 9-10).

The specimen is a skeletal muscle tissue (claims 10 and 11 on column 59).

Grobet et al., do not explicitly disclose that their method employs a probe sequence which hybridizes to SEQ ID No. 6, 8, wherein said probe consists of SEQ ID No. 10 or 12.

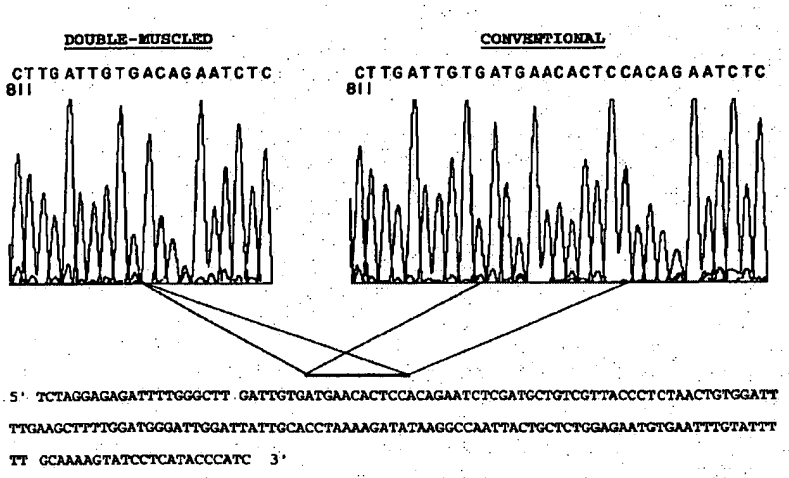
Grobet et al. do not explicitly disclose a kit comprising, in a first container, a nucleic acid hybridization probe which hybridizes to SEQ ID Numbers 6 or 8 (claim 43), wherein said nucleic acid hybridization probe is selected from SEQ ID Numbers 10 or 11 (claim 44), said kit further comprising amplification polymerase and dNTPs (claim 45), detectable means (claim 46).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to employ the nucleic acid hybridization probe of SEQ ID No. 10, which hybridizes to a nucleic acid sequence of SEQ ID No. 6, in the method of Grobet et al., thereby arriving at the claimed invention for the following reasons.

Grobet et al. state that their detection method – the step of detecting the DNA encoding an allelic protein lacking the activity – correlates that a subject has muscular hyperplasia (or increased muscle mass) (see column 3, lines 1-8).

Grobet et al. are also explicit in disclosing that this DNA encoding an allelic protein, is an 11-base pair deletion (column 4, lines 52-55).

Figure 2A of the sequence disclosed by Grobet et al. compares the location of this 11-bp deletion with respect to the wild-type sequence (see below):



Grobet et al. disclose a mutant myostatin nucleic acid sequence (SEQ ID NO: 3), which lacks the above- 11-bp deletion (see below):

```
ACA CCA AAA AGA TCT AGG AGA GAT TTT GGG CTT GAT TGT GAC AGA ATC      871
Thr Pro Lys Arg Ser Arg Arg Asp Phe Gly Leu Asp Cys Asp Arg Ile
260                 265                 270                 275


TCG ATG CTG TCG TTA CCC TCT AAC TGT GGA TTT TGAAGCTTTT              914
Ser Met Leu Ser Leu Pro Ser Asn Cys Gly Phe
```

Therefore, while Grobet et al. do not explicitly disclose a probe sequence that consists of SEQ ID Number 10, which hybridizes to SEQ ID Number 6, one of ordinary skill in the art at the time the invention was made would have been clearly motivated to derive an oligonucleotide probe

hybridizing to this deletion site so as to identify whether a subject is predisposed or is having increased muscle mass as a result of the disclosed mutation with a reasonable expectation of success. Given that a mutation is known, it is well-within the purview of an ordinarily skilled artisan to derive an oligonucleotide probe of the requisite length so as to detect the mutation with high specificity.

With regard to claims 43 and 44, one of ordinary skill in the art would have been motivated to package the above derived oligonucleotide probe in view of the conventionality of kits in the analytical arts for the advantages of convenience, cost-effectiveness, matched and/or preweighed components, etc.

With regard to claims 45 and 46, Grobet et al. discloses that their method employs amplification of the nucleic acid segment comprising the mutation (column 14, lines 22-25) via PCR and that the amplified target is labeled (column 11, lines 1-3). It is well known in the art that PCR (polymerase chain reaction) employs an amplification polymerase such as Taq polymerase. Hence, it would have been obvious to one of ordinary skill in the art at the time the invention was made to also package the polymerase and labels in to the same kit for the same benefit of convenience, cost-effectiveness, matched and/or preweighed components.

The invention as claimed is *prima facie* obvious over Grobet et al.

Claims 31, 32, 34, 35, 43-50, and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kambadur et al. (Genome Research September 1997, vol. 7, no. 9, pages 910-916) in view of Valent et al. (Molecular Microbiology, July 1997, vol. 25, no. 1, pages 53-64).

Kambadur et al. disclose a method of detecting the presence of a target myostatin variant nucleic acid sequence from a bovine sample (Belgian Blue and Piedmontese; page 915, 1st column, bottom paragraph; and page 915, 2nd column 1st paragraph), wherein the artisans identify 11 base pair

deletion in Belgian Blue myostatin gene and G to A substitution in exon 3 of Piedmontese myostatin gene (Abstract; page 914, 1st column), mutations which are homozygous and responsible for increased muscle mass (page 914, 1st column).

The detection is achieved by amplifying a segment containing the mutation from a myostatin gene via use of primers flanking the mutation (page 915, 2nd column 3rd paragraph) and sequencing the amplified product (page 915, 2nd column, 4th paragraph), thereby clearly anticipating claims 25-28 and 42.

Kambadur et al. explicitly state that the 11-bp deletion would result in a truncated encoded protein (page 914, 1st column also see Figure 1C; and page 913 for its description).

Kambadur et al. state that G to A substitution occurs at position 941 of the coding region, it appears that the mutation is the same mutation.

The sample employed in the disclosed method is from Belgian Blue and Piedmontese which are of the bovine species.

The sample employed by Kambadur et al. is biceps femoris muscle which inherently comprises skeletal muscles (page 915, 1st column, bottom paragraph).

Kambadur et al. do not explicitly teach oligonucleotides which hybridize to flanking regions of the target nucleic acid, wherein said flanking regions to which the oligonucleotides hybridize are SEQ ID NO: 1 and 2 (claim 31), wherein said oligonucleotides are SEQ ID Numbers 3 and 4 (claim 32).

Kambadur et al. do not explicitly disclose that the target nucleic acid is detected using a nucleic acid hybridization probe, wherein the probe hybridizes to SEQ ID Number 6 or 8 (claim 34), wherein said probe is SEQ ID Number 10 or 12 (claim 35).

Kambadur et al. do not explicitly teach a kit comprising the probe which hybridizes to a target nucleic acid, wherein the probe hybridizes to SEQ ID No. 6 or 8 (claim 43), wherein said probe is SEQ ID No. 10 or 12 (claim 44).

Kambadur et al. do not teach said kit further comprising an amplification polymerase and dNTPs (claim 45), a detectable means (claim 46).

Kambadur et al. do not teach said kit further comprising oligonucleotides which hybridize to flanking regions of the target nucleic acid, wherein said flanking regions to which the oligonucleotides hybridize is SEQ ID NO: 1 and 2 (claim 47), wherein said oligonucleotides are SEQ ID Numbers 3 and 4 (claim 48).

Kambadur et al. do not teach a kit comprising oligonucleotides which hybridize to flanking regions of the target nucleic acid, wherein said flanking regions to which the oligonucleotides hybridize is SEQ ID NO: 1 and 2 (claim 49), wherein said oligonucleotides are SEQ ID Numbers 3 and 4 (claims 50 and 53).

Valent et al. disclose a well known method amplifying a target nucleic acid via use of a pair of primers flanking the target nucleic acid, wherein said pair of primers comprise a BamHI recognition site at their 5' ends, for the purpose of cloning and sequencing reaction (page 62, 1st column, see 2nd paragraph). In particular, Valent et al. employ a primer comprising the following sequence, 5'-CGCGGATCC-target sequence-3' (BamHI recognition underlined).

It would have been *prima facie* obvious to one of ordinary skill in the art to combine the teachings of Kambadur et al. with the teachings of Valent et al., thereby arriving at the claimed invention for the following reasons.

While Kambadur et al. do not explicitly disclose a probe sequence that consists of SEQ ID Number 10, which hybridizes to SEQ ID Number 6, one of ordinary skill in the art at the time the

invention was made would have been clearly motivated to derive an oligonucleotide probe hybridizing to the deletion site (11 bp deletion mutation) disclosed by Kambadur, so as to identify whether a subject is predisposed or is having increased muscle mass as a result of the disclosed mutation with a reasonable expectation of success. Given that a mutation is known, it is well-within the purview of an ordinarily skilled artisan to derive an oligonucleotide probe of the requisite length so as to detect the mutation with high specificity.

In addition, given the fact that myostatin gene was already known in the art, one of ordinary skill in the art would have been able to derive oligonucleotide primers flanking the known mutations disclosed by Kambadur et al., so as to amplify and detect the presence of the mutations for the purpose of diagnosis.

With regard to the restriction enzyme recognition sequence on the 5' end of the primers, the practice of adding restriction recognition site into the primers for the purpose of cloning and sequencing the amplified sequence is well known and established as evidenced by Valent et al. Hence, one of ordinary skill in the art at the time the invention was made would have had a clear expectation of success at combining the teachings of Kambadur et al. and Valenti et al., thereby arriving at the invention as claimed.

With regard to claims 43 and 44, one of ordinary skill in the art would have been motivated to package the above derived oligonucleotide probe in view of the conventionality of kits in the analytical arts for the advantages of convenience, cost-effectiveness, matched and/or preweighed components, etc.

With regard to claims 45-50, Grobet et al. discloses that their method employs amplification of the nucleic acid segment comprising the mutation (column 14, lines 22-25) via PCR and that the amplified target is labeled (column 11, lines 1-3). It is well known in the art that PCR (polymerase

chain reaction) employs an amplification polymerase such as Taq polymerase. Hence, it would have been obvious to one of ordinary skill in the art at the time the invention was made to also package the polymerase and labels in to the same kit for the same benefit of convenience, cost-effectiveness, matched and/or preweighed components.

For the above reasons, the invention as claimed is *prima facie* obvious over the cited references.

Double Patenting

Applicant is advised that should claim 50 be found allowable, claim 53 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof.

Claim 50 is drawn to a kit comprising oligonucleotides SEQ ID Number 3 and 4.

Claim 53 is also drawn to a kit comprising oligonucleotides SEQ ID Numbers 3 and 4.

When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Conclusion

No claims are allowed.

Applicants are advised to file a terminal disclaimer over U.S. Patent No. 6,673,534.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner is

on flex-time schedule and can best be reached from 8:30 a.m. to 4:30 p.m. The Examiner can also be reached via e-mail to Young.Kim@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Young J. Kim
Patent Examiner
Art Unit 1637
1/26/2006

YOUNG J. KIM
PATENT EXAMINER

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